The disclosure provides a bispecific antigen binding molecule, comprising
(a) at least one antigen binding domain capable of specific binding to CD40, and
(b) at least one antigen binding domain capable of specific binding to a target cell antigen.

In one aspect, the disclosure provides a bispecific antigen binding molecule, comprising

(a) at least ~~one antigen binding domain~~two Fab fragments capable of specific binding to CD40, and

(b) ~~at least~~ one antigen binding domain capable of specific binding to FAP comprising a heavy chain variable region (VHFAP) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:4, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:5, and a light chain variable region (VLFAP) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:6, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:7, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8~~ connected to the C-terminus of the Fc region~~, and
(c) a Fc region composed of a first and a second subunit capable of stable association, wherein the Fc region is an IgG1 Fc region or an IgG4 Fc region and comprises one or more amino acid substitution that reduces the binding affinity of the antibody to an Fc receptor and/or effector function, and wherein the CDR-L3 of the antigen binding domain is connected to the C-terminus of the Fc region.

(v) in delaying progression of cancer,
(vi) in prolonging the survival of a patient suffering from cancer,
(vii) in the treatment of infections.

~~In another aspect, provided is the bispecific antigen binding molecule of the disclosure, or the pharmaceutical composition of the disclosure, for use in the treatment of infections.~~

In a specific aspect, provided is the bispecific antigen binding molecule as described herein before or the pharmaceutical composition of the disclosure, for use in the treatment of cancer. In another aspect, the present disclosure provides use of the bispecific antigen binding molecule as described herein, or the pharmaceutical composition as described herein, in the manufacture of a medicament for the treatment of cancer. The disclosure provides the bispecific antigen binding molecule as described herein before for use in the treatment of cancer, wherein the bispecific antigen binding molecule is administered in combination with a chemotherapeutic agent, radiation and/ or other agents for use in cancer immunotherapy. In another aspect, the disclosure provides the bispecific antigen binding molecule of the disclosure or the pharmaceutical composition of the disclosure for use in combination cancer therapy, wherein the bispecific antigen binding molecule is to be administered in combination with a chemotherapeutic agent, radiation and/ or other agents for use in cancer immunotherapy. In another aspect, the present disclosure provides use of the bispecific antigen binding molecule as described herein or the pharmaceutical composition as described herein in the manufacture of a medicament for use in combination cancer therapy, wherein the bispecific antigen binding molecule is to be administered in combination with a chemotherapeutic agent, radiation and/ or other agents for use in cancer immunotherapy. Provided is the bispecific antigen binding molecule as described herein before or the pharmaceutical composition of the disclosure, for use in up-regulating or prolonging cytotoxic T cell activity.

The disclosure provides a method of inhibiting the growth of tumor cells in an individual comprising administering to the individual an effective amount of the bispecific antigen binding molecule as described herein before, or the pharmaceutical composition of the disclosure, to inhibit the growth of the tumor cells. The disclosure provides a method of treating or delaying cancer in an individual comprising administering to the individual an effective amount of the bispecific antigen binding molecule as described herein before, or the pharmaceutical composition of the disclosure.

## Claims

1. A bispecific antigen binding molecule, comprising

(a) at least ~~one antigen binding domain~~two Fab fragments capable of specific binding to CD40, and

(b) ~~at least~~ one antigen binding domain capable of specific binding to FAP comprising a heavy chain variable region ($V_H$FAP) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:3, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:4, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:5, and a light chain variable region ($V_L$FAP) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:6, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:7, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:8 ~~connected to the C-terminus of the Fc region~~, and

(c) a Fc region composed of a first and a second subunit capable of stable association, wherein the Fc region is an IgG1 Fc region or an IgG4 Fc region and comprises one or more amino acid substitution that reduces the binding affinity of the antibody to an Fc receptor and/or effector function, and wherein the CDR-L3 of the antigen binding domain is connected to the C-terminus of the Fc region.

~~2. The bispecific antigen binding molecule of claim 1, additionally comprising~~

~~(c) a Fc region composed of a first and a second subunit capable of stable association.~~

~~3~~2. The bispecific antigen binding molecule of claim 1 ~~or claim 2~~, wherein the antigen binding domain capable of specific binding to CD40 binds to a polypeptide comprising, or consisting of, the amino acid sequence of SEQ ID NO:1.

~~4~~3. The bispecific antigen binding molecule of ~~any one of claims 1 to 3~~claim 1 or 2, wherein the antigen binding domain capable of specific binding to FAP comprises

~~(a)~~ a heavy chain variable region ($V_H$FAP) comprising an amino acid sequence ~~that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence~~ of SEQ ID NO:9, and a light chain variable region ($V_L$FAP) comprising an amino acid sequence ~~that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence~~ of SEQ ID NO:10~~, or~~

~~(b) a heavy chain variable region ($V_H$FAP) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:17, and a light chain variable region ($V_L$FAP) comprising an amino acid sequence that is at least about 95%, 96%, 97%, 98%, 99% or 100% identical to the amino acid sequence of SEQ ID NO:18~~.

~~54~~54. The bispecific antigen binding molecule of any one of claims 1 to ~~43~~43, wherein the antigen binding domain capable of specific binding to CD40 comprises a heavy chain variable region ($V_H$CD40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:19, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:20, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:21, and a light chain variable region ($V_L$CD40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:22, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:23, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:24.

~~65~~65. The bispecific antigen binding molecule of any one of claims 1 to ~~43~~43, wherein the antigen binding domain capable of specific binding to CD40 comprises a heavy chain variable region ($V_H$CD40) comprising (i) CDR-H1 comprising the amino acid sequence of SEQ ID NO:27, (ii) CDR-H2 comprising the amino acid sequence of SEQ ID NO:28, and (iii) CDR-H3 comprising the amino acid sequence of SEQ ID NO:29, and a light chain variable region ($V_L$CD40) comprising (iv) CDR-L1 comprising the amino acid sequence of SEQ ID NO:30, (v) CDR-L2 comprising the amino acid sequence of SEQ ID NO:31, and (vi) CDR-L3 comprising the amino acid sequence of SEQ ID NO:32.

~~76~~76. The bispecific antigen binding molecule of any one of claims 1 to ~~65~~65, wherein the antigen binding domain capable of specific binding to CD40 comprises

(a) a VH comprising the amino acid sequence of SEQ ID NO:25 and a VL comprising the amino acid sequence of SEQ ID NO:26, or

(b) a VH comprising the amino acid sequence of SEQ ID NO:33 and a VL comprising the amino acid sequence of SEQ ID NO:34.

~~87~~87. The bispecific antigen binding molecule of any one of claims 1 to ~~54~~54, wherein the antigen binding domain capable of specific binding to CD40 comprises

(i) a heavy chain variable region ($V_H$CD40) comprising an amino acid sequence selected from the group consisting of SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173 and SEQ ID NO:174, and

(ii) a light chain variable region ($V_L$CD40) comprising the amino acid sequence selected from the group consisting of SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, and SEQ ID NO:178.

~~98~~98. The bispecific antigen binding molecule of any one of claims 1 to ~~54~~54, wherein the antigen binding domain capable of specific binding to CD40 comprises

(i) a heavy chain variable region ($V_H$CD40) comprising an amino acid sequence selected from the group consisting of SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183 and SEQ ID NO:184, and

(ii) a light chain variable region ($V_L$CD40) comprising the amino acid sequence selected from the group consisting of SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187, and SEQ ID NO:188.

~~10~~9. The bispecific antigen binding molecule of any one of claims 1 to ~~5~~ 4 or ~~8~~7, wherein the antigen binding domain capable of specific binding to CD40 comprises

(a) a VH comprising the amino acid sequence of SEQ ID NO:171 and a VL comprising the amino acid sequence of SEQ ID NO:175, or

(b) a VH comprising the amino acid sequence of SEQ ID NO:173 and a VL comprising the amino acid sequence of SEQ ID NO:177, or

(c) a VH comprising the amino acid sequence of SEQ ID NO:174 and a VL comprising the amino acid sequence of SEQ ID NO:178, or

(d) a VH comprising the amino acid sequence of SEQ ID NO:171 and a VL comprising the amino acid sequence of SEQ ID NO:177, or

(e) a VH comprising the amino acid sequence of SEQ ID NO:171 and a VL comprising the amino acid sequence of SEQ ID NO:178, or

(f) a VH comprising the amino acid sequence of SEQ ID NO:173 and a VL comprising the amino acid sequence of SEQ ID NO:175, or

(g) a VH comprising the amino acid sequence of SEQ ID NO:173 and a VL comprising the amino acid sequence of SEQ ID NO:178, or

(h) a VH comprising the amino acid sequence of SEQ ID NO:174 and a VL comprising the amino acid sequence of SEQ ID NO:175, or

(i) a VH comprising the amino acid sequence of SEQ ID NO:174 and a VL comprising the amino acid sequence of SEQ ID NO:177, or

(j) a VH comprising the amino acid sequence of SEQ ID NO:171 and a VL comprising the amino acid sequence of SEQ ID NO:176, or

(k) a VH comprising the amino acid sequence of SEQ ID NO:172 and a VL comprising the amino acid sequence of SEQ ID NO:175, or

(l) a VH comprising the amino acid sequence of SEQ ID NO:172 and a VL comprising the amino acid sequence of SEQ ID NO:176, or

(m) a VH comprising the amino acid sequence of SEQ ID NO:172 and a VL comprising the amino acid sequence of SEQ ID NO:177, or

(n) a VH comprising the amino acid sequence of SEQ ID NO:172 and a VL comprising the amino acid sequence of SEQ ID NO:178, or

(o) a VH comprising the amino acid sequence of SEQ ID NO:173 and a VL comprising the amino acid sequence of SEQ ID NO:176, or

(p) a VH comprising the amino acid sequence of SEQ ID NO:174 and a VL comprising the amino acid sequence of SEQ ID NO:176.

~~11~~10. The bispecific antigen binding molecule of any one of claims 1 to ~~5~~ 4 or ~~8~~ 7 or ~~10~~9, wherein the antigen binding domain capable of specific binding to CD40 comprises a VH comprising the amino acid sequence of SEQ ID NO:171 and a VL comprising the amino acid sequence of SEQ ID NO:175.

~~12~~11. The bispecific antigen binding molecule of any one of claims 1 to ~~5~~ 4 or ~~9~~8, wherein the antigen binding domain capable of specific binding to CD40 comprises

(a) a VH comprising the amino acid sequence of SEQ ID NO:179 and a VL comprising the amino acid sequence of SEQ ID NO:185, or

(b) a VH comprising the amino acid sequence of SEQ ID NO:180 and a VL comprising the amino acid sequence of SEQ ID NO:185, or

(c) a VH comprising the amino acid sequence of SEQ ID NO:181 and a VL comprising the amino acid sequence of SEQ ID NO:185, or

(d) a VH comprising the amino acid sequence of SEQ ID NO:182 and a VL comprising the amino acid sequence of SEQ ID NO:185, or

(e) a VH comprising the amino acid sequence of SEQ ID NO:179 and a VL comprising the amino acid sequence of SEQ ID NO:186, or

(f) a VH comprising the amino acid sequence of SEQ ID NO:180 and a VL comprising the amino acid sequence of SEQ ID NO:186, or

(g) a VH comprising the amino acid sequence of SEQ ID NO:181 and a VL comprising the amino acid sequence of SEQ ID NO:186, or

(h) a VH comprising the amino acid sequence of SEQ ID NO:182 and a VL comprising the amino acid sequence of SEQ ID NO:186, or

(i) a VH comprising the amino acid sequence of SEQ ID NO:183 and a VL comprising the amino acid sequence of SEQ ID NO:187, or

(j) a VH comprising the amino acid sequence of SEQ ID NO:183 and a VL comprising the amino acid sequence of SEQ ID NO:188, or

(k) a VH comprising the amino acid sequence of SEQ ID NO:184 and a VL comprising the amino acid sequence of SEQ ID NO:187, or

(l) a VH comprising the amino acid sequence of SEQ ID NO:184 and a VL comprising the amino acid sequence of SEQ ID NO:188.

~~13~~12. The bispecific antigen binding molecule of any one of claims 1 to ~~5~~ 4 or ~~9~~ 8 or ~~12~~11, wherein the antigen binding domain capable of specific binding to CD40 comprises a VH comprising the amino acid sequence of SEQ ID NO:179 and a VL comprising the amino acid sequence of SEQ ID NO:185 or wherein the antigen binding domain capable of specific binding to CD40 comprises a VH comprising the amino acid sequence of SEQ ID NO:182 and a VL comprising the amino acid sequence of SEQ ID NO:185.

~~14~~13. The bispecific antigen binding molecule of any one of claims 1 to ~~5~~4, comprising

(i) at least one antigen binding domain capable of specific binding to CD40, comprising a heavy chain variable region ($V_H$CD40) comprising an amino acid sequence selected from the group consisting of SEQ ID NO:171, SEQ ID NO:172, SEQ ID NO:173, SEQ ID NO:174, SEQ ID NO:179, SEQ ID NO:180, SEQ ID NO:181, SEQ ID NO:182, SEQ ID NO:183 and SEQ ID NO:184, and a light chain variable region ($V_L$CD40) comprising an amino acid sequence selected from the group consisting of SEQ ID NO:175, SEQ ID NO:176, SEQ ID NO:177, SEQ ID NO:178, SEQ ID NO:185, SEQ ID NO:186, SEQ ID NO:187 and SEQ ID NO:188, and

(ii) at least one antigen binding domain capable of specific binding to FAP, comprising a heavy chain variable region ($V_H$FAP) comprising an amino acid sequence of SEQ ID NO:9 and a light chain variable region ($V_L$FAP) comprising an amino acid sequence of SEQ ID NO:10~~, or a heavy chain variable region ($V_H$FAP) comprising an amino acid sequence of SEQ ID NO:17 and a light chain variable region ($V_L$FAP) comprising an amino acid sequence of SEQ ID NO:18~~.

~~15. The bispecific antigen binding molecule of any one of claims 2 to 14, wherein the Fc region is an IgG, particularly an IgG1 Fc region or an IgG4 Fc region and wherein the Fc region comprises one or more amino acid substitution that reduces the binding affinity of the antibody to an Fc receptor and/or effector function.~~

~~16~~14. The bispecific antigen binding molecule of any one of claims ~~2 to 15~~1 to 13, wherein the Fc region is (i) of human IgG1 subclass with the amino acid mutations L234A, L235A and P329G (numbering according to Kabat EU index), or (ii) of mouse IgG1 subclass with the amino acid mutations D265A and P329G (numbering according to Kabat EU index).

~~17. The bispecific antigen binding molecule of any one of claims 1 to 16, wherein the bispecific antigen binding molecule comprises~~

~~(a) at least two Fab fragments capable of specific binding to CD40 connected to a Fc region, and~~

~~(b) one antigen binding domain capable of specific binding to FAP connected to the C-terminus of the Fc region.~~

~~18~~15. The bispecific antigen binding molecule of any one of claims 1 to ~~17~~14, wherein the bispecific antigen binding molecule comprises

(a) at least two Fab fragments capable of specific binding to CD40 connected to a Fc region, and

(b) a cross-fab fragment capable of specific binding to FAP connected to the C-terminus of the Fc region.

~~19~~16. The bispecific antigen binding molecule of any one of claims 1 to ~~17~~15, wherein the bispecific antigen binding molecule comprises four Fab fragments capable of specific binding to CD40.

~~20~~17. Polynucleotide encoding the bispecific antigen binding molecule of any one of claims 1 to ~~19~~16.

~~21~~18. An expression vector comprising the polynucleotide of claim ~~20~~17.

~~22~~19. A host cell comprising polynucleotide of claim ~~18~~ 17 or the expression vector of claim ~~21~~18.

~~23~~20. A method of producing a bispecific antigen binding molecule, comprising culturing the host cell of claim ~~22~~ 19 under conditions suitable for the expression of the bispecific antigen binding molecule, and isolating the bispecific antigen binding molecule.

~~24~~21. A pharmaceutical composition comprising the bispecific antigen binding molecule of any one of claims 1 to ~~19~~ 16 and at least one pharmaceutically acceptable excipient.

~~25~~22. The bispecific antigen binding molecule of any one of claims 1 to ~~19~~16, or the pharmaceutical composition of claim ~~24~~21, for use as a medicament.

~~26. The bispecific antigen binding molecule of any one of claims 1 to 19, or the pharmaceutical composition of claim 24, for use in the treatment of infections.~~

~~27~~23. The bispecific antigen binding molecule of any one of claims 1 to ~~19~~16, or the pharmaceutical composition of claim ~~24~~21, for use in the treatment of cancer.

~~28~~24. The bispecific antigen binding molecule according to any one of claims 1 to ~~19~~ 16 or the pharmaceutical composition according to claim ~~24~~ 21 for use in combination cancer therapy, wherein the bispecific antigen binding molecule is to be administered in combination with a chemotherapeutic agent, radiation and/ or other agents for use in cancer immunotherapy.

25. Use of the bispecific antigen binding molecule of any one of claims 1 to 16, or the pharmaceutical composition of claim 21, in the manufacture of a medicament for the treatment of cancer.

26. Use of the bispecific antigen binding molecule according to any one of claims 1 to 16 or the pharmaceutical composition according to claim 21 in the manufacture of a medicament for use in combination cancer therapy, wherein the bispecific antigen binding molecule is to be administered in combination with a chemotherapeutic agent, radiation and/ or other agents for use in cancer immunotherapy.

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